AMENDMENTS TO THE CLAIMS:

Please amend claims 1 and 27. This listing of claims replaces all prior versions and listings of claims in the application.

LISTING OF CLAIMS:

1. (Currently Amended) A high throughput process for the identification of a protein that differs in a predetermined property or activity from a target protein, comprising:

(a) producing a plurality of separate sets of nucleic acid molecules that encode modified forms of a target protein, wherein:

the nucleic acid molecules in each set are produced by changing one codon in the target protein to a pre-selected codon, whereby the nucleic acid molecules in each set encode proteins that differ from the encoded proteins in another set by one amino acid;

a sufficient number of sets of nucleic acid molecules are produced so that each encoded amino acid residue in the encoded protein is replaced with a pre-selected amino acid along the full-length of the encoded protein so that all positions along the full-length of the protein are individually modified for screening, and each nucleic acid molecule encodes a protein that differs by one amino acid from the target protein; and

all nucleic acid molecules in a set encode the same modified protein;

(b) individually introducing each set of nucleic acid molecules into host cells to produce an addressable array of host cells, whereby the identity of each set of nucleic acid molecules in host cells of each locus in the array is known, wherein the cells of each locus of the addressable array contain the same modified nucleic acid molecules;

(c) expressing the encoded proteins, whereby a plurality of separate sets of proteins encoded by the nucleic acid molecules are produced and all positions along the full-length of the protein are individually modified, wherein:

all of the encoded proteins in each set have the same modification; and

the proteins in each set differ from the proteins in another set by one amino acid and from the target protein by one amino acid; and

(d) individually screening each set of encoded proteins to identify one or more proteins that have a predetermined property that differs from the target , wherein:

each identified protein is designated a hit;

each hit contains a mutation designated a hit position; and

the predetermined property or activity is selected from among a chemical, a physical and a biological property or an activity of the target protein;

(e) modifying the nucleic acid molecules that encode the hits to produce sets of nucleic acid molecules that encode modified hits, wherein:

the modified hits are produced by systematically and individually replacing each codon that is a hit position with a codon encoding another amino acid to produce nucleic acid molecules each differing by at least one codon and encoding modified hits; each set of nucleic acid molecules is individually designed and synthesized., whereby:

a sufficient number of sets are produced to produce encoded proteins in which every hit is separately replaced with all other amino acids, and the encoded protein in each set differs from the encoded protein each other set and the target protein by one amino acid ;

the identity of each set of nucleic acid molecules in host cells of each locus in the array is known and wherein the cells of each locus of the addressable array contain the same modified nucleic acid molecules;

(f) separately introducing each set of nucleic molecules that encodes the modified hits into cells to produce an addressable array of cells, whereby the identity of each encoded protein at each locus in the array is known and expressing the protein encoded by the introduced nucleic acid molecules; and

(g) screening all cells that contain the expressed protein by individually screening each set of cells that contains the nucleic acid molecules that encode the modified hits to identify one or more nucleic acid molecules that encode(s) a protein or the coded protein that has/have ~~a~~ the predetermined property or activity that differs from the target protein and has properties that differ from the original hits, wherein each such protein is designated a lead,

wherein each and all of steps (a)-(g) are performed in an automated high throughput format whereby each molecule is individually designed, produced, screened and tested in the high throughput format .

2. (Original) The process of claim 1, wherein each set of nucleic acid molecules is individually designed and synthesized.

3. (Previously Presented) The process of claim 2, wherein each set is deposited at a locus on a solid support configured as an array.

4. Cancelled.

5. (Original) The process of claim 1, wherein the array comprises a solid support with loci for containing or retaining cells; and each locus contains one set of cells.

6. (Original) The process of claim 1, wherein the array comprises a solid support with wells for containing or retaining cells; and each well contains one set of cells.

7. (Original) The process of claim 1, wherein the nucleic acid molecules comprise viral vectors; and the cells are eukaryotic cells that are transduced with the vectors.

8. (Original) The process of claim 1, wherein the nucleic acid molecules comprise plasmids and the cells are bacterial cells.

9.-13. Cancelled.

14. (Previously Presented) The method of claim 1, wherein the pre-selected amino acid is selected from among Ala (A), Ser (S), Pro (P) and Gly (G).

15. (Previously Presented) The method of claim 1, wherein the pre-selected amino acid is selected from among Arg (R), Asn (N), Asp (D), Cys (C), Gln (Q), Glu (E), His (H), Ile (I), Leu (L), Lys (K), Met (M), Phe (F), Thr (T), Trp (W), Tyr (Y) and Val (V).

16. Cancelled.

17. (Previously Presented) The method of claim 1, further comprising:

recombining the nucleic acid molecules encoding the leads;

introducing those nucleic acid molecules into cells; and

screening the cells to identify nucleic acid molecules that encode new leads that exhibit a greater change in a property or in an activity than the leads identified in claim 1.

18. (Original) The method of claim 17, wherein the recombining is two, three or more up to all of the nucleic acids encoding the leads.

19. (Original) The method of claim 17, wherein the recombining is effected by a method selected from among nucleic acid shuffling, recombination, site-directed or random mutagenesis and *de novo* synthesis.

20. Cancelled.

21. Cancelled.

22. (Previously Presented) The process of claim 1, wherein

the predetermined property or activity is selected from among a chemical, a physical and a biological property or activity of the target protein, wherein the change in a

predetermined property comprises a change in an activity of the target protein that is at least about 10%, 20%, 30%, 40% or 50% compared to the unmodified target protein.

23. (Previously Presented) The process of claim 1, wherein

the predetermined property or an activity is selected from among a chemical, a physical and a biological property or an activity of the target protein, wherein the change in the predetermined property or an activity comprises a change in a property or an activity of the target protein that is at least about 75%, 100%, 200%, 500% or 1000% compared to the unmodified target protein.

24. (Previously Presented) The process of claim 1, wherein:

in step (b) the nucleic acid molecules comprise viral vectors, and the methods further comprises assessing the titer of the viral vectors in each set of cells; and

the predetermined property or an activity is selected from among a chemical, a physical and a biological property of the target protein.

25. (Original) The method of claim 24, wherein titering is effected by real time virus titering, comprising:

(i) incubating the nucleic acid molecules or a vector (biological agent) comprising the nucleic acid molecules at an initial concentration C, which is the unknown titer, with the host cells at a constant known concentration, D;

(ii) measuring at successive times, an output signal, i;

(iii) determining the time tβ, wherein:

tβ corresponds to i=β;

$\beta_{min} < \beta < \beta_{max}$;

β_{min} and β_{max} correspond to values of i at the inflection point of the curve i=f(t), for the minimal and maximal values, respectively, of the concentrations of a reference biological agent for which the curve tβ=f(c) is predetermined; and

(iv) determining the initial concentration C.

26. (Original) The method of claim 24, wherein titering is effected by Tagged Replication and Expression Enhancement, comprising:

(i) incubating with host cells a reporter virus vector with a titering virus of unknown titer, wherein the titering virus increases or decreases the output signal from the reporter virus; and

(ii) measuring the output signal of the reporter virus and determining the titer of the reporter virus;

(iii) determining the titer of the interfering virus by comparing the titer of the reporter virus in the presence and absence of the interfering virus.

27. (Currently Amended) A high throughput process for the identification of a protein that differs in a predetermined property from a target protein, comprising:

(a) producing a population of sets of nucleic acid molecules that encode modified forms of a target protein, wherein:

each encoded modified protein in a set differs from the encoded proteins in each other set and from the target protein by one amino acid;

a sufficient number of sets of nucleic acid molecules are produced so that each encoded amino acid residue in the encoded protein is replaced with a pre-selected amino acid along the full-length of the encoded protein so that all positions along the full-length of the protein are individually modified for screening, and each nucleic acid molecule encodes a protein that differs by one amino acid from the target protein; and

the members of each set encode the same modified protein;

(b) individually, but at the same time, introducing each set of nucleic acid molecules into host cells and expressing the encoded protein, wherein:

the host cells are organized in an addressable array, whereby the identity of each nucleic acid molecule at each locus in the array is known;

each set of nucleic acid molecules is introduced into host cells at a different locus of the array, whereby the identity of each set of nucleic acid molecules in host cells at each locus of the array is known, wherein:

the cells of each locus of the addressable array contain the same modified nucleic acid molecules;

all encoded proteins in each set contain the same modification; and

the proteins in each set differ from the proteins in another set by one amino acid and from the target protein by one amino acid; and

(c) individually, but at the same time, screening the sets of encoded proteins to identify one or more proteins, designated hits, that have a predetermined property that differs from the target protein is/are identified, wherein:

each identified protein is designated a hit;

each hit contains a mutation designated a hit position; and

the predetermined property is selected from among a chemical, a physical and a biological property of the target protein;

the nucleic acid molecules comprise viral vectors; and the cells are eukaryotic cells that are transduced with the vectors;

(d) modifying the nucleic acid molecules that encode the hits to produce a set of nucleic acid molecules that encode modified hits, wherein each nucleic acid is in a viral vector;

(e) introducing each set of nucleic acids that encode the modified hits into cells; and

(f) individually, but at the same time, screening the sets of cells that contain the nucleic acid molecules that encode the modified hits to identify one or more cells that encodes a protein that has a predetermined property or activity that differs from the target protein and has properties that differ from the original hits, wherein each such protein is designated a lead,

wherein each and all of steps (a)-(f) are performed in an automated highthroughput format whereby each molecule is individually designed, produced, screened and tested in the high throughput format. .

28. (Original) The method of claim 27, wherein at step (f) the titer of the viral vectors in each set of cells is determined.

29. (Original) The method of claim 28, wherein the target protein is a protein involved in viral replication.

30. (Previously Presented) The process of claim 1,

wherein the performance of the screened proteins is evaluated by a Hill analysis or by fitting the output signal to a curve representative of the interaction of the target protein and a test compound.

31. (Previously Presented) The process of claim 30, wherein the Hill analysis, comprises:

(a) preparing a sample of each nucleic acid molecule or a plasmid or vector that comprises each nucleic acid molecule (biological agent), wherein each sample is obtained by a serial dilution of the molecules or vector or plasmid at a concentration R1;

(b) incubating each sample of the dilution obtained in (a) with the host cells (target cells) at a constant concentration R2;

(c) determining a P product from the reaction R1 + R2, at a t moment, in each the sample; and

(d) preparing a theoretical curve H from the experimental points R1 and P, for each biological agent by iterative approximation of parameters of the reaction R1 + R2 $\rightarrow$ P, at the t moment, in accordance with the equation:

$$P = P_{max} (\pi R1)^r / (\kappa + (\pi R1)^r) \qquad r=1,\ldots,n \qquad (2)$$

in which:

R1 represents the biological agent concentration in a sample from the scale;

R2 is concentration of target cells (in vitro or in vivo)

P (output) represents the product from the reaction R1 + R2 at a t moment;

P_{max} represents the reaction maximal capacity;

κ represents, at a constant R2 concentration, the biological system for responding to the biological agent (resistance constant R2);

r represents a dependent coefficient of R1 and corresponds to the Hill coefficient; and

π represents the intrinsic power of the R1 biological agent to induce a response in the biological system (P production at the t moment); and

(e) sorting the κ and π values obtained in (d) for each protein encoded by the nucleic acid molecules or plasmids or vectors and the cells, and then ranking according to the values thereof.

32. (Previously Presented) A process of claim 1 that is automated.

33. (Original) The process of claim 32 that is computer-controlled.

34-41. (Cancelled)

42. Cancelled.

43. (Previously Presented) The method of claim 27, wherein the pre-selected amino acid is selected from among Ala (A), Ser (S), Pro (P) and Gly (G).

44. (Currently Amended) The method of claim 27, wherein the pre-selected amino acid is selected from among encoding Arg (R), Asn (N), Asp (D), Cys (C), Gln (Q), Glu (E), His (H), Ile (I), Leu (L), Lys (K), Met (M), Phe (F), Thr (T), Trp (W), Tyr (Y) and Val (V).